REMARKS

Status of the Claims

Claims 1, 4, 6-11, 13-15, and 37-53 were pending in the application.

Claims 1, 4, 6-11, 13-15, and 37-53 were rejected.

Applicants request that claims 9, 42, and 51 be amended.

Upon entry of this amendment, claims 1, 4, 6-11, 13-15, and 37-53 will be pending.

Summary of the Amendment

Applicants request that claims 9, 42, and 51 be amended to correct an obvious typographical error. The term "by" has been incorporated into the claims to modify the term "detected." Entry of the amendment places the claims in better condition for allowance or appeal. No substantive issues are raised by the amendment. Support for the amendment appear on page 14, line 6, of the specification.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1, 4, 6-11, 13-15, and 37-53 stand rejected under 35. U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Office asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office asserts that:

> [I] t is again noted applicants fail to describe a representative number of species. The genus is comprised of about 20,000 known human genes of which an unknown number are epithelial cell markers. Applicants have

> adequately described only 26, or less than 0.2%. Less than 0.2% is not a representative number of species for this genus. Applicants argue that the percentage of 0.2 is dramatically lower than a real estimate because this percentage is based on all of the known human genes rather than those currently known to be differentiation-specific antigens of epithelial cells. This argument is not persuasive because 26 is still not representative of the genus.

(Office Action, page 9). Applicants respectfully disagree.

The rejection is not supported by the Official Action. It is well established that the examiner has the initial burden of presenting evidence or reasoning to explain why person skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). In rejecting the claims, the examiner must set forth express findings of fact regarding the analysis required under 35 U.S.C. §112, first paragraph. MPEP Section 2163 III(A); See *In re Rasmussen*, 650 F.2d 1212, 1214, 221 USPQ 323, 326.

The Office has failed to set forth any findings of fact or evidence to support the rejection. Despite Applicants contention that the genus is not 20,000 known human genes, the Office asserts that "26 species is still not a representative genus." (Office Action, page 9). The Office has not provided any other evidence to support this position. The Office has not provided the correct number of members of the genus. Rather, the Office asserts a mere conclusory statement.

The Office has not established that the claimed invention does not meet the written description requirement. Failing to do so, the burden is not properly shifted to Applicants.

The Office's reliance on *The Regents of the University of California v. Eli Lilly* 43 USPQ2d 1398 in support of this position is also misguided. In *Eli Lilly*, the court held

claims of a patent owned by the University of California directed to cDNA encoding human insulin and vertebrate insulin from patents were invalid for failing to meet the written description requirement because the patentees only disclosed a single species of cDNA, that which encoded rat insulin. The court reasoned that because there was unpredictability in **performance** of certain species or subcombinations other than those specifically enumerated, the disclosure was insufficient to place one skilled in the art in possession of a genus. The facts in the instant application are greatly distinguishable from those in *Eli Lilly*. The instantly claimed subject matter relates to a method of identifying the presence of mRNAs encoding disseminated epithelial cell markers, not to the mRNAs themselves. The performance of the undisclosed species can be predicted based upon the performance of the disclosed species.

The fact that all of the mRNAs that encode disseminated epithelial cell markers are not disclosed is irrelevant to whether the method claim is sufficiently supported by the specification. The recent case law which is informative of the proper application of *Eli Lilly* indicates that the proper analysis for determining whether or not a representative number of species has been disclosed turns on whether or not the performance of the disclosed species would be representative of the genus.

In the recent decision by the Court of Appeals for the Federal Circuit in *Bilstad v. Wakalopulos* 386 F.3d 1116, 1125 (Fed. Cir. 2004), the court found that the Board failed to apply the proper standard for determining the sufficiency of the written description requirement. The court stated that that disclosure of a species may be sufficient written description support for a later claimed genus including that species if the difference between members of the group is such that the person skilled in the art would readily discern that other members of the genus would perform similarly to the disclosed members. In the instant application, the person skilled in the art would readily discern that other members of the genus would perform similarly to the disclosed members.

In *Amgen Inc. v. Hoechst Marion Roussel, Inc*, 314 F.3d 1313 (Fed. Cir. 2003). the Federal Circuit distinguished its decision from *Eli Lilly* "because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." The claim terms at issue in the instant application are similarly not new or unknown to those having ordinarily skilled artisans who would readily understand and recognize the claimed subject matter. The court in *Amgen* noted that unlike the facts in *Eli Lilly,* one having ordinary skill in the art could visualize or recognize the identity of the members of the genus. Such is the case in the instant application as well.

The claimed invention involves a method of identifying mRNAs from disseminated epithelial cell markers. The specification provides an actual reduction to practice of a way to isolate several species of the claimed genus by depletion of CD34+ cells. Those skilled in the art would expect that all of the species within the genus would retain the function of the several species identified as epithelial cell markers because each species must be isolated by exactly the same means. Therefore, the predictability of the species within the genus is high. The claimed genus of mRNAs is defined by the presence of structure represented by guanylyl cyclase C, Cdx-1, Cdx-2, sucrase isomaltase, lactase, carbonic anhydrase, prostate specific antigen, prostate specific membrane antigen, cytokeratin 18, cytokeratin 19, cytokeratin 20, ErbB2, Erb-B3, epithelial mucin-1, epithelial mucin-18, gastrointestinal tumor associated antigen 733.2, desmoplakin I, epithelial glycoprotein 40, tyrosinase, thyroglobulin, tyrosine hydroxylase, and neuron-specific glycoprotein. One skilled in the art would recognize that the applicant was in possession of structural feature shared by each of the members of the claimed genus at the time of filing. The species shown in the specification is therefore representative of the species within the claimed genus unlike *Eli Lilly*.

Applicants' specification provides the sequence information for eleven different mRNA transcripts of the genus in addition to their origin/expression in disseminated

epithelial cells on page 18 of the specification. The Office has also already agreed that the "Applicants have adequately described 26 [epithelial cell markers]." (Office action, page 9). These facts are starkly different than the facts of *Eli Lilly* where the specification provided only one rat cDNA sequence as a representative example for a much larger genus including ***all*** vertebrate insulin cDNAs and ***all*** mammalian insulin cDNAs. Therefore the suggestion that the recitation of 26 members of a genus as insufficient is not consistent with the holding of *Eli Lilly*. In view of the above discussion, Applicants respectfully assert that *Eli Lilly* cannot be applied dispositively in support of the Office's position.

Even if the Office had met its burden of reasoning or evidence, which Applicants do not concede, the rejection under 35 U.S.C. §112, first paragraph, would still be improper because the Office has failed to identify the correct genus of claim 4 and its associated dependent claims.

Claim 4 recites a method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of a) eliminating CD34+ cells from the sample using an anti-CD34 antibody based affinity process; and b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen; wherein the disseminated epithelial cell marker is selected from the group consisting of guanylyl cyclase C, Cdx-1, Cdx-2, sucrase isomaltase, lactase, carbonic anhydrase, prostate specific antigen, prostate specific membrane antigen, cytokeratin 18, cytokeratin 19, cytokeratin 20, ErbB2, Erb-B3, epithelial mucin-1, epithelial mucin-18, gastrointestinal tumor associated antigen 733.2, desmoplakin I, epithelial glycoprotein 40, tyrosinase, thyroglobulin, tyrosine hydroxylase, and neuron-specific glycoprotein; wherein said detection of said mRNA indicates the presence of a disseminated epithelial cell marker. The genus of cell markers identified in the claim includes guanylyl cyclase C, Cdx-1, Cdx-2, sucrase isomaltase, lactase, carbonic anhydrase, prostate specific antigen, prostate specific membrane antigen, cytokeratin 18, cytokeratin 19, cytokeratin

20, ErbB2, Erb-B3, epithelial mucin-1, epithelial mucin-18, gastrointestinal tumor associated antigen 733.2, desmoplakin I, epithelial glycoprotein 40, tyrosinase, thyroglobulin, tyrosine hydroxylase, and neuron-specific glycoprotein. Therefore, the Office's characterization of the genus of claim 4 and its dependent claims is clearly in error.

Nevertheless, as mentioned above, Applicants have described species related to the genus of claim throughout the specification but specifically mention the sequence of eleven of these markers in a non-limiting example at page 18 of the present specification. As for listing both structure and function of the genus members, eleven species disclosed is approximately 50% of the members of the disclosed genus in claim 4. This, again, is in stark contrast to the Office's position which alleges only 0.2% of the genus members disclosed.

The level of knowledge and skill in the art is such that skilled artisans would expect disseminated epithelial cell markers other than those species set forth in the specification to perform in the same manner as the disclosed species. Moreover, those of ordinary skill in the art readily envisage the genus of mRNAs encoding disseminated epithelial cell markers. Based on the knowledge in the art and the correlation between the source of the mRNA of the claimed invention of isolation, one skilled in the art would have recognized that the description of the disseminated epithelial cell markers would have put the applicant in possession of the genus mRNA sequences of the claimed invention at the time of filing.

The specification provides sufficient written description of the present invention. Applicants respectfully request that the rejection of claims 1, 4, 6-11, 13-15, and 37-53 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 1, 4, 6-11, 13-15, and 37-53 stand rejected as being unpatentable over Ts'o, *et. al.*, in view of Elliot, *et. al.* Applicants respectfully disagree.

Ts'o discloses removal of white blood cells from a sample prior to detection of mRNA encoding PSA or PSMA to reduce false positives.

Eliot describes elimination of CD34+ cells from a sample using an anti-CD34 antibody based kit.

It is asserted that because CD34+ cells are among those which are removed in T'so, it would be obvious to combine T'so with the teachings of Eliot which describe using anti-CD34 antibodies to remove CD34+ cells. Applicants respectfully disagree.

One skilled in the art would not consider using anti-CD34 antibodies to remove CD34+ cells. One skilled in the art, attempting to eliminate false positives, would not have seen a benefit to using anti-CD34 antibodies to remove CD34+ cells. The identification of the problem caused by the presence of CD34+ cells was not recognized prior to Applicants' invention. Accordingly, the modification of T'so with using anti-CD34 antibodies to remove CD34+ cells taught by Eliot would not have been obvious to one skilled in the art.

The removal of multiple types of cells taught by T'so is not interchangeable with the selective removal of CD34+ cells. The only reason to do so is based upon Applicants' disclosure, which is impermissible. One skilled in the art would not substitute the crude extraction of white cells with the use of a specific antibody directed to CD34+ cells absent the teachings in Applicants specification. The law is clear that Applicants' teachings cannot be used in determining if an invention is obvious.

Nothing in Ts'o or Eliot suggest that CD34+ cells are the source of the problem of false positives. One of ordinary skill in the art would not find the claimed invention obvious in view of the combination of teachings of Ts'o and Eliot.

With respect to the subject matter of claims 37-47, Ts'o teaches away from the claimed invention. Claims 37-47 refer to the sample being mononuclear cells isolated

from blood. That is, claims 37-47 refer to removing CD34+ cells using anti-CD34 antibodies from mononuclear cells isolated from blood. Ts'o teaches removal of blood mononuclear cells from the sample to be analyzed for the presence of the marker. One skilled in the art would conclude Ts'o teaches away from the instant invention as defined by claims 37-47. Regarding the passages in Ts'o which describe removal of specific cell types as opposed to the teachings to remove all blood mononuclear cells from the sample to be analyzed, one skilled in the art would not expect that removal of CD34+ cells would eliminate false positives as disclosed in the instant application.

Claims 1, 4, 6-11, 13, and 37-45 are not obvious in view of Ts'o and Eliot. Applicants respectfully request that the rejection of claims 1, 4, 6-11, 13, and 37-45 under 35 U.S.C. §103(a) as being unpatentable over Ts'o in view of Eliot be withdrawn.

Claims 14, 15, 46, and 47 stand rejected as being unpatentable over Ts'o, *et. al.*, in view of Elliot, *et. al.* and further in view of Waldman, *et. al.* Applicants respectfully disagree.

Ts'o and Eliot are discussed above.

Waldman discloses GCC as a marker for colorectal cancer.

Waldman does not suggest that CD34+ cells are the source of the false positives. Waldman does not make up for the deficiency in the combination of Ts'o and Eliot. For the reasons set forth above, one skilled in the art would not conclude that the claimed invention is obvious in the absence of Applicants' disclose, which cannot be used. Moreover, with respect to claim 47, Ts'o teaches away from the subject matter of the claim.

Claims 14, 15, 46, and 47 are not obvious in view of Ts'o, Eliot, and further in view of Waldman. Applicants respectfully request that the rejection of claims 14, 15, 46, and 47 under 35 U.S.C. §103(a) as being unpatentable over Ts'o in view of Eliot and further in view of Waldman be withdrawn.

Conclusion

Claims 1, 4, 6-11, 13-15, and 37-53 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-0436.

Respectfully Submitted,

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